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09/042,460	03/16/1998	GREGG B. MORIN	015389003110	5004

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	

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31

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/042,460	MORIN ET AL.	
	Examiner	Art Unit	
	S. Kaushal	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-28 and 31-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,23-26,28 and 32-34* is/are rejected.

7)☒ Claim(s) *21,22,27 and 31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's response filed .on 12/07/01 and Dr. Choy-Pik Chiu's declaration has been acknowledged.

Claims 20, 21, 28 were amended.
Claims 31-34 were newly filed claims
Claims 20-28 and 31-34 were pending and were examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The references cited herein are of record in a prior Office action.

*If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED.*

Applicant's arguments filed 12/07/01 have been fully considered but they are not persuasive, for the reasons of record as set forth in the earlier office action (Paper No.25, 04/25/01).

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by an application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: After applicant's amendment on 02/14/00 the instant application claims priority only to US App. No. 08/979, 742 filed 11/26/97, and **not to the other US or PCT applications** as stated in the declaration. Appropriate correction is required.

Claim Objections

Claims 32-34 are objected to because of the following informalities: The instant claims recites limitation "shown in figure 5" and fails to recite the required SEQ ID NO.

> 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences regardless of whether a given sequence is also embedded in the text of the description or claims of an application.(see MPEP 2422.03)
> Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 20, 23, 26 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, **had possession of the claimed invention** and for the reasons of record set forth in Official action mailed 04/25/01.

The applicant argues that species disclosed (SEQ ID NO:2) is representative of the genus because all members have at least 90% structural identity with the reference compound. The applicant further argues that example-9 indicates that claims reciting stringent hybridization conditions and functional activity meet the written description requirements. Similarly, example 14 indicates the claims reciting a degree of sequence homology and functional activity meet the written description requirements (response, page 5, ¶ 3).

However, this is not found persuasive because the scope of instant claims (after recent amendment) encompasses any polynucleotides encoding **any and all non-natural and/or natural telomerase reverse transcriptase protein**, which has at least 90% sequence identity to amino acid sequences of SEQ ID NO:2. The invention as claimed encompass a polynucleotide, which encodes a telomerase reverse transcriptase protein, wherein at least 10% of amino acid sequences are added, deleted or substituted over the entire length of the polypeptide. The variation also encompasses the conserved motifs that are germane to the telomerase reverse transcriptase activity. At best the specification only discloses the nucleic acid encoding SEQ ID

NO:2 (mouse) having telomerase like activity and fails to disclose a single variants of SEQ ID No:2 that have telomerase reverse transcriptase protein-like activity. As stated in the earlier office action, the general knowledge in the art concerning telomerase is that telomerase-complex consists of TERT protein, RNA component and other TRT associated proteins. Furthermore, TERT protein consists of several conserved motifs that are required for the telomerase activity (Lundblad, PNAS 95:8415-8416, 1998). The specification as filed fails to disclose any common attributes of variants of SEQ ID NO:2 that retain TERT activity. In addition, it is unclear how any change (10% variation over the entire length) in the amino acid sequences would not result in any change in the formation of telomerase-complex formation that would eventually effect the telomerase activity.

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In addition possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention Pfaff v. Wells Electronics, Inc 48 USPQ2d 1641, 1646 (1998). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claims 20, 23, 26 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide encoding mouse mTERT protein of SEQ ID NO:2, does not reasonably provide enablement for non-natural and/or natural TERT proteins that have at least 90% sequence identity to SEQ ID NO:2 and has telomerase catalytic activity when associated with a telomerase RNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the invention **commensurate in scope** with these claims, for the same reasons of record as set forth in the official action mailed on 04/25/01.

The applicant argues that the specification provides number of assays for determining telomerase activity and one skill in the art may readily make variants of SEQ ID NO:2 by introducing mutations and testing the mutants for telomerase activity (response, page 5, ¶ 4).

However, this is not found persuasive because the scope of instant claims encompass an isolated nucleic acid molecule encoding **a telomerase reverse transcriptase protein and its natural or non-natural variants**, which has at least 90% sequence identity to amino acid sequences of SEQ ID NO:2. The instant specification as filed fails to disclose any and all polynucleotide sequences that has 90% sequence identity to SEQ ID NO: 2 and has telomerase like activity. The invention as claimed encompass a polynucleotide, which encodes a telomerase reverse transcriptase, wherein 10% of amino acid sequences are added, deleted or substituted over the entire length of the polypeptide. The variation also encompasses the conserved motifs that are germane to the telomerase reverse transcriptase activity. At best the specification only discloses the nucleic acid encoding SEQ ID NO:2 having mouse mTERT activity and fails to disclose a single variants of SEQ ID No:2 that have any mTERT like activity. As stated in the earlier office action, the general knowledge in the art concerning telomerase is that telomerase-complex consists of TERT protein, RNA component and other TRT associated proteins. Furthermore, TERT protein consists of several conserved motifs that are required for the telomerase activity (Lundblad, PNAS 95:8415-8416, 1998, *ref of record*). The specification as filed fails to identify the functional attributes of individual variants other than SEQ ID NO: 2. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The recited SEQ ID NO(s) are simply compute-generated hypothesis because no biological function has been established. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues.

The applicant further argues that US Patents 6284477, 6287839, 6291220, 6297356, and 6297367 all claim polypeptides or polynucleotides on the basis of 80% or 90% homology to a representative sequence in combination with functional activity (response, page 6, ¶1).

Applicant's argument alone cannot take place of evidence lacking in the record. Each patent application is examined on its own merit and is considered enabled in view of its own disclosure. The issue is not whether the other application support their claims but whether this application supports its claims "[i]t is immaterial whether similar claims have been allowed to other" In re Gialito 188USPQ 645,648 (CCPA 1976).

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The courts have clearly stated that: "A specification did not disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). The general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".* Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997).

In instant case screening of any and all natural and non-natural telomerasere reverse transcriptase variants, wherein at least 10% amino acid are added substituted and /or deleted in the disclosed SEQ ID NO:2 is not considered routine. The applicant fails to point out where in the specification there is support for extensive making and testing of any and all natural and non-natural variants of telomerase as claimed. Making and testing a point mutation is significantly different from the making and testing an amino acid sequences wherein at least 10% amino acids are added, deleted and/or substituted. The number of possible scenarios increase geometrically with increase in percent non-identity. Such making and testing is nothing more than an invitation

variants as claimed. One has to engage in extensive making and testing in order to obtain variants that meet the requirements for the claimed telomerase activity. This is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The applicant has not presented enablement commensurate in scope with the claims.

Claims 23-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an **isolated cell** comprising the polynucleotide that encodes SEQ ID NO:2 in-vitro, does not reasonably provide enablement for any cell comprising the polynucleotide that encodes SEQ ID NO:2 or its variant (as claimed) in-vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims for the same reasons of record as set forth in the earlier official action mailed on the 04/25/01*.

Claim 28 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, **to make and/or use** the invention, for the same reasons of record as set forth in the official action mailed on 04/25/01*.

The applicant collectively argues that *claims 23-25 and 28 are enabled because claims to isolated, purified or recombinant polynucleotides are enabled in any context including in living cells, especially in-vivo and in the construction of a knockout mouse. The applicant further argues that use of prophetic examples does not make a patent non-enabling (response, page 6, ¶ 3-4). The applicant further argues that Dr. Choy-Pik Chiu's declaration explains that mice are being generated that are heterologous and homozygous of mTERT gene according to description in this application.

However, this is found unpersuasive because the scope of instant claim encompasses a cell that is transformed in vivo, therefore the invention as claimed falls in the realm of gene therapy. The earlier office action clearly stated that the Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations (Rosenberg et al, Science 287:1751, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997). The specification fails to disclose the delivery of polynucleotides as claimed in-vivo using viral or non-viral vectors via any and all routes of administration. Besides degradation the viral or non-viral vectors binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets. Considering the unpredictability in the gene therapy art one skill in the art would unable to exercise the invention as claimed without undue amount of experimentation. The amount of experimentation required would include making of any and all viral and non-viral vectors encoding any and all variants of telomerase nucleotide sequences and successful delivery of the vectors to the target cells that would lead to telomerase expression in vivo.

In addition claim 28 encompass not only an isolated mouse cell but also include a mouse cell derived from a transgenic mouse (*which is non-elected subject matter, see office action 07/05/00, page 2*) wherein the endogenous mTERT gene has been mutated. The earlier office action clearly states that the applicants fails to disclose even a single transfected cell wherein any and all components of telomerase complex have been knocked out by recombinant means and an exogenous mTERT gene have been transfected. At best example-4 teaches the electroporation of pmTERTKO vector in to WW6 ES cells but falls short of disclosing a single cell clone wherein the mTERT gene has been mutated (see example-4, page 114, line 27-31). Similarly, the specification discloses the injection of WW6 ES clones into C57BL/6 blastocytes, wherein the mTERT gene has been knocked out but fails to disclose a single founder animal exhibiting the required phenotype. The earlier office action clearly states that state of transgenic art at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. The phenotype examined in a transgenic and knock out model is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. (see Wood. Comp. Med. 50(1): 12-15, 2000, Sigmund, Arterioscler. Throm. Vasc.

Biol.20:1425-1429, 2000, Kappel et al. Current Opinion in Biotechnology 3:558-553 1992, Rossant et al , Phil. Trans. R. Soc Lond. B. 339:137-254, 1993, Viville, in Transgenic Animals, Houdebine (eds), Harwood academic publishers, France. pp307-321, 1997). The instant specification fails to fails to disclose a single founder animal that exhibits the required phenotype. wherein the endogenous telomerase gene has been mutated by any recombinant means. Dr. Choy-Pik Chiu's declaration relies on publications that were published after the filing date of instant application, which does not enable instant specification for full scope of invention as claimed.

Applicant's argument alone cannot take place of evidence lacking in the record. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The courts have clearly stated that: "A specification did not disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). However, general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".* Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997).

In instant case genetic engineering of cells in-vivo via method of gene therapy and making of transgenic knock-out mouse to obtain the modified cells are not considered routine and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue

amount of experimentation to exercise the invention as claimed. Therefore, Applicant has not presented enablement commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 is indefinite to because the metes and bound of instant claim are unclear. The instant claim depends upon a canceled claim "claim 1". Therefore, it is unclear what the instant claim further limits.

Conclusion

No claims are allowed.

Claims 20, 23-26, 28 and 32-34 are rejected.

Claim 31 is objected.

Claims 21-22 and 27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten independent form including all of the limitation of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Irem.Yucel can be reached on (703) 305-1998. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Zeta Adams, whose telephone number is (703) 305-3291.

S. Kaushal
PATENT EXAMINER

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER